second paragraph.

II. The 35 U.S.C. § 112 First Paragraph Rejections of the Claims

In the Office Action mailed March 13, 2002, the Examiner rejected claims 8, 11-12 and 20-21 under 35 U.S.C. § 112, first paragraph, alleging that those claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. In the same Office Action, the Examiner rejected claims 8, 11-12 and 20-21 under 35 U.S.C. § 112, first paragraph, alleging that the specification does not enable the production of a lipooligosaccharide (LOS) using a *rfe* gene different from the *E. coli rfe*. In the Advisory Action mailed August 20, 2002, the Examiner withdrew all of the rejections of claims under 35 U.S.C. § 112, first paragraph.

III. The 35 U.S.C. § 103(a) Rejection of the Claims

In the Office Action mailed March 13, 2002, the Examiner rejected claims 6-8, 11-12 and 18-21 under 35 U.S.C. § 103(a) as being unpatentable over McLaughlin *et al.* (*Journal of Endotoxin Research*, *1*, 165 (1994)) in view of Alexander *et al.* (*J. of Bacteriology*, *176*, 7079 (1994)). The Examiner maintained this rejection in the Advisory Action mailed August 20, 2002. As this rejection may be maintained with respect to the pending claims, it is respectfully traversed.

Claim 11 recites a process for the production of a *Haemophilus influenzae*-specific lipooligosaccharide (LOS) which comprises the steps of (a) growing in a culture medium gram-negative bacteria comprising (i) a core lipid structure containing a terminal heptose and (ii) a DNA sequence comprising an *rfe* gene, and (iii) an isolated DNA sequence comprising a lipooligosaccharide-synthesis gene (*lsg*) from *Haemophilus influenzae*, wherein the protein encoded by the *rfe* gene is expressed and adds an acceptor molecule to the heptose molecule to synthesize an oligosaccharide; and (b) recovering the *H. influenzae*-specific LOS from the culture medium. Claims 6-8, 12, 18-19 and 22 depend from claim 11.

Claim 20 recites a method of modifying a terminal heptose of a lipopolysaccharide (LPS)

or lipooligosaccharide (LOS) core structure of a gram-negative bacterial species containing an *rfe* gene comprising regulating the protein encoded by the *rfe* gene with a protein encoded by an isolated *lsgG* gene from *Haemophilus influenzae* in order to catalyze transferring N-acetyl glucosamine onto the terminal heptose. Claims 23-29 depend from claim 20.

Claim 21 recites a process for the production of a complex carbohydrate comprising the steps of: (a) growing in a culture medium gram-negative bacteria comprising (i) a core lipid structure containing a terminal heptose and (ii) a DNA sequence comprising an *rfe* gene, and (iii) an isolated DNA sequence comprising a liposaccharide-synthesis gene G (*lsgG*) from *Haemophilus influenzae*, wherein the protein encoded by the *rfe* gene is expressed and adds an acceptor molecule to the heptose molecule to synthesize complex carbohydrate; and (b) recovering the complex carbohydrate from the culture medium. Claims 23-29 depend from claim 21.

To establish a *prima facie* case of obviousness, the Examiner has the burden to establish three basic elements. First, the Examiner must establish that there is some suggestion or motivation, either in the cited references themselves or in the knowledge generally available to an art worker, to modify the reference or to combine reference teachings so as to arrive at the claimed invention. Second, the Examiner must establish that there is a reasonable expectation of success. Finally, the Examiner must establish that the prior art reference teaches or suggests all the claim limitations. M.P.E.P. § 2143.

Applicant respectfully maintains that the Examiner has failed to establish that either the cited documents or the knowledge generally available to an art worker at the time the application was filed provides a suggestion or motivation to combine or modify the cited documents so as to arrive at Applicant's claimed invention. Applicant also maintains that the Examiner has failed to establish that the cited documents teach or suggest all of the elements of Applicant's claimed invention.

Applicant respectfully submits that the Examiner has not established that either the cited documents or the knowledge generally available to an art worker at the time the application was filed provides a suggestion or motivation to combine or modify the cited documents so as to arrive at Applicant's claimed invention. The teaching or suggestion to arrive at the claimed

invention must be found in the prior art, not in Applicant's disclosure. M.P.E.P. § 2143 citing with favor, *In re Vaeck*, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991); emphasis added. The Examiner must provide specific, objective evidence of record for a finding of a suggestion or motivation to combine the reference teachings and must explain the reasoning by which the evidence is deemed to support such a finding. *In re Sang Su Lee*, 277 F.3d 1338, 61 U.S.P.Q.2D 1430 (Fed. Cir. 2002); emphasis added. Mere conclusory statements do not fulfill the Examiner's burden. *Id.*; underline added. As has been stated (*Id.* at 1433):

> [t]he factual inquiry whether to combine references must be thorough and searching. It must be based on objective evidence of record. This precedent has been reinforced in myriad decisions, and cannot be dispensed with. *See, e.g., Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1124-25, 56 U.S.P.Q.2d 1456, 1459 (Fed. Cir. 2000) ("a showing of a suggestion, teaching, or motivation to combine the prior art references is an 'essential component of an obviousness holding'") (*quoting C.R. Bard, Inc., v. M3 Systems, Inc.*, 157 F.3d 1340, 1352, 48 U.S.P.Q.2d 1225, 1232 (Fed. Cir. 1998)); *In re Dembiczak*, 175 F.3d 994, 999, 50 U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999) ("Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references."); *In re Dance*, 160 F.3d 1339, 1343, 48 U.S.P.Q.2d 1635, 1637 (Fed. Cir. 1998) (there must be some motivation, suggestion, or teaching of the desirability of making the specific combination that was made by the applicant); *In re Fine*, 837 F.2d 1071, 1075, 5 U.S.P.Q.2d 1596, 1600 (Fed. Cir. 1988) ("'teachings of references can be combined only if there is some suggestion or incentive to do so.'") (emphasis in original) (*quoting ACS Hosp. Sys., Inc. v. Montefiore Hosp.*, 732 F.2d 1572, 1577, 221 U.S.P.Q. 929, 933 (Fed. Cir. 1984)).

Applicant maintains that the Examiner has not provided appropriate evidence or explanation for a suggestion or motivation to combine the cited documents. Instead, in the Office Action mailed March 13, 2002, the Examiner made the conclusory statement: "Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to make lipooligosaccharides with *E. coli* K-12 expressing an *E. coli rfe* and an *H. influenzae lsg*." The Examiner followed that statement with: "The motivation of making *H. influenzae*-specific lipooligosaccharides is to produce the lipooligosaccharides in large amounts to effectively obtain oligosaccharides, useful in developing vaccines and in

identification of *H. influenzae* bacteria itself." In the Advisory Action mailed August 20, 2002, the Examiner states that "the motivation to combine the reference of Alexander et al. and McLaughlin et al. is to introduce the rfe gene to the teachings of Alexander et al. since the rfe enzyme is essential for the fi[r]st step in the biosynthesis of lipooligosaccharides." However, neither of the cited documents teach that "the rfe enzyme is essential for the fist step in the biosynthesis of lipooligosaccharides." McLaughlin *et al.* does not even mention the *rfe* gene. Alexander *et al.* at best teaches that the *rfe* gene appears to have a role in the synthesis of the O-specific polysaccharides in *E. coli* strains O7, O18, O75 and O111 (page 7079). Thus, the Examiner has not provided a proper suggestion or motivation to combine or modify the cited documents to arrive at Applicant's invention.

In contrast, Applicant's specification provides a template to arrive at the claimed invention. The specification, for example starting at page 21, teaches that the assembly of the chimeric structure in *E. coli* is controlled by the unique interaction of *E. coli rfe* and *H. influenzae lsg*. In this interaction the regulator, *lsg*, increases the expression of *rfe*. This results in the addition of an N-acetylglucosamine to the carrier lipid, undecaprenol pyrophosphate. The remainder of the carbohydrate structure is then assembled on this N-acetylglucosamine-undecaprenol complex, and then ligated to the terminal heptose. Thus, *lsgG* increases expression of *rfe*, thereby resulting in an abundance of the undecaprenol-N-acetylglucosamine complex, which allows the other Lsg transferases to construct the chimeric structure.

To render an invention obvious, the combination of the cited art must teach or suggest the claimed invention and provide a reasonable expectation of success in preparing the claimed invention. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991); *In re O'Farrell*, 853 F.2d 894, 7 U.S.P.Q.2d 1673 (Fed. Cir. 1988). Absent Applicant's template, Applicant maintains that the Examiner has not established that the art worker would have a suggestion or motivation to combine or modify the cited documents so as to arrive at Applicant's claimed invention.

Furthermore, even if combined, Applicant maintains that the Examiner has failed to establish that the cited documents teach or suggest all of the elements of Applicant's claimed

invention. For example, McLaughlin *et al.*, of which co-Applicant M. Apicella is co-author, simply presents a DNA sequence analysis of the *Haemophilus influenzae lsgG* locus. McLaughlin *et al.* does not describe how the *lsgG* locus functions in *E. coli*. McLaughlin *et al.* also does not describe how a chimeric complex carbohydrate might be assembled. Furthermore, McLaughlin *et al* does not even suggest that the modified core might be an assembly platform for other carbohydrate constructs.

Alexander *et al.* examines the role the *rfe* gene in the assembly of the O-antigen in *E. coli*. In contrast, the claimed invention involves a unique role for *rfe*. Under the proper regulatory stimulus by *Haemophilus influenzae lsgG*, *rfe* can be upregulated in expression to allow assembly of the chimeric carbohydrates on the *E. coli* LPS core antigen. None of this is described in Alexander *et al.*

Furthermore, as discussed above, neither Alexander *et al.* or McLaughlin *et al.* teach or suggest that a protein encoded by an *rfe* gene adds an acceptor molecule to the terminal heptose on a core lipid structure of a gram-negative bacteria (claims 11 and 21), much less that the protein encoded by the rfe *gene* can be regulated by a protein encoded by an isolated *lsgG* gene from *Haemophilus influenzae* in order to catalyze transferring N-acetyl glucosamine onto the terminal heptose (claim 20).

Thus, the Examiner has failed to establish that Alexander *et al.* or McLaughlin *et al.*, either alone or taken in combination, teach the present claimed invention.

For the reasons described hereinabove, Applicant submits that the Examiner has not make out a *prima facie* case of obviousness because the Examiner has not established that the art provides a suggestion or motivation to combine the documents. Applicant also asserts that the Examiner has failed to establish that, even if combined, the cited documents teach or suggest all of the elements of Applicant's claimed invention. Therefore, Applicant respectfully requests that this rejection under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSION

Applicant respectfully submits that the claims are in condition for allowance and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney (612-373-6961) to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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The undersigned hereby certifies that this correspondence is being transmitted by facsimile (FAX NO. 703-872-9306) to: Attn.: Examiner Yong Pak, GAU 1652, Commissioner of Patents, Washington. D.C. 20231, on this 31st day of October, 2002.

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